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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/062,483	02/05/2002	Baoshan Ku	3519-0115P	2815

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EXAMINER

KIM, VICKIE Y

ART UNIT	PAPER NUMBER
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1614

DATE MAILED: 09/08/2003

8

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/062,483

Applicant(s)

KU ET AL.

Examiner

Vickie Kim

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☐ Responsive to communication(s) filed on ____.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-20 is/are pending in the application.
- 4a) Of the above claim(s) 15-20 is/are withdrawn from consideration.
- 5) ☐ Claim(s) ____ is/are allowed.
- 6) ☒ Claim(s) 1-14 is/are rejected.
- 7) ☐ Claim(s) ____ is/are objected to.
- 8) ☐ Claim(s) ____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on ____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on ____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. ____.
 - ☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892) 4) ☐ Interview Summary (PTO-413) Paper No(s). ____
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948) 5) ☐ Notice of Informal Patent Application (PTO-152)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 4. 6) ☐ Other:

DETAILED ACTION***Election acknowledged***

Applicants affirmation on the election with traverse of Group I, claims 1-20 is acknowledged. Applicant requested s traverse the restriction requirement on the grounds that there would be no burden in searching the entire application. This argument is not persuasive, as not all groups encompassed by the application would be define a contribution which each of the inventions, considered as a whole, makes over the prior art. For instance, morphine and tetrodotoxin is well known material used in medical field individually and in combination (see Okwuasaba et al(abstract, 1976) or Anagnostakis(abstract, 1998), see PTO-892) wherein the utility of said combination is different from the invention of Group I. As mentioned in previous office action, each invention is found to be patentably distinct subject matter proven in numerous patent literatures. Furthermore, even if there were unity of classification, the search of the entire application in patent and non-patent literature (a significant part of the thorough examination) would be burdensome due to the reasons mentioned in previous office action(e.g. patentably distinct subject matter proven in numerous patent literature). Therefore the restriction requirement is maintained and made FINAL.

Status of Application

The claims 1-20 are pending, and presented for the examination.

The elected claims 1-14 are presented for the examination and the non-elected claims 15-20 are withdrawn from the consideration.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 1-14 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for tetrodotoxin, saxitoxin, or its derivatives recited in the specification, does not reasonably provide enablement for all the possible compounds binding SS1 or SS2 subunit of sodium channel. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

For rejections under 35 USC 112, first paragraph, the following factors must be considered(In re Wands, 8 USPQ2d 1400, 1404 (CAFC, 1988)):

- 1) Nature of invention
- 2) State of prior art
- 3) Level of ordinary skill in the art
- 4) Level of predictability in the art
- 5) Amount of direction and guidance provided by the inventor
- 6) Existence of working examples
- 7) Breadth of claims
- 8)Quantity of experimentation needed to make or use the invention based on the content of the disclosure.

See below:

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1) Nature of the invention

Instant invention is directed to a method of producing analgesia using a synergically analgesic effective combination of an opioid analgesic agent and a compound that binds to the SS1 or SS2 subunit of a sodium channel in a pharmaceutically suitable vehicle.

2) State of the prior art.

The references cited in the instant specification teaches about toxin compound such as tetrodotoxin and its analogs; or saxitoxin and its analogs that are functionally equivalent to each other and may be substitutable, useful together in the claimed invention. However, the references do not provide any assay method that determines which compound has the sodium channel(SS1/SS2) blocking activity. Even if it is the conventional knowledge to determine such activity, the references do not indicate that all the compounds which bind to SS1/SS2 sodium channel blocker has analgesic activity, see WO 95/23132. WO'132 teaches a compound having SS1/SS2 sodium channel blocking activity and its use in the treatment of ischemic brain and heart diseases, epilepsy and amyotrophic lateral sclerosis, see abstract and claim 1. Thus, at the time of the invention, not all the compounds encompassed by the instant application are considered be useful in the claimed invention.

3) Level of ordinary skill in the art.

The level of ordinary skill in the art is high.

4) Level of predictability in the art.

The unpredictability of the pharmaceutical art is very high. In fact, the courts have made a distinct between mechanical elements function the same in different circumstances, yielding predictable results, chemical and biological compounds often

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react unpredictably under different circumstances. Nationwide Chem. Corp. v. Wright, 458 F. Supp. 828, 839, 192 USPQ 95, 105 (M.D. Fla. 1976); Aff'd 584 F.2d 714, 200 USPQ 257 (5th Cir. 1978); In re Fischer, 427 F.2d 833, 839, 166 USPQ 10, 24 (CCPA 1970). The art pertaining to the physiological and pharmacological activity of a chemical or biological compound is considered to be highly unpredictable.

5) Amount of direction and guidance provided by the inventor.

The amount of guidance or direction needed to enable the invention is inversely related to the degree of predictability in the art. In re Fischer, 839, 166 USPQ 24. Thus, although a single embodiment may provide broad enablement in cases involving predictable factors, such as mechanical or electrical elements, in cases involving unpredictable factors, such as most chemical reactions and physiological activity, more teaching or guidance is required. In re Fischer 427 F.2d 839, 166 USPQ 24; Ex Parte Hitzeman, 9 USPQ 2d 1823.

For example, the Federal circuit determined that, given the unpredictability of the physiological activity of viruses or microorganisms, a specification requires more than a general description and a single embodiment to provide an enabling disclosure for a method of protecting an organism against virus or microorganism infection. In re Wright, 999 F.2d 1562-63 USPQ2d 1575.

In the instant case, applicant made a mere assertion at page 10, lines 3-8. Applicant states that TTX and STX possess similar modes of action and toxicity, therefore, the inventors suggest that STX is also synergistic with the analgesic activity of opioids at similar dosage ranges. The examiner assumes that applicant applied the same analogy to their analogs. The instant specification contemplates few working examples using TTX. Even if, applicant's allegation is true where TTX and STX can be substitutable to each other, it would not been proper to extend this assumption to other

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compounds that do not share any common characteristics with the said toxin compounds.

As mentioned earlier, applicant fails to provide any assay method or guidance to determine the sodium channel blocking activity or analgesic activity.

A disclosure should contain representative examples, which provide reasonable assurance to one skilled in the art that the compounds fall within the scope of claims will possess the alleged activity.

6) Existence of working examples.

As stated above, the specification does not disclose any working examples of SS1/SS2 sodium channel blocker other than TTX(tetrodotoxin).

7) Breadth of claims.

The claims are extremely broad due to the vast number of possible compounds that are obtained from numerous synthesis and their analgesic activity.

8) Quantity of experimentation needed to make or use the invention based on the content of the disclosure.

The specification did not enable any person skilled in the art to which it pertains to make or use the invention commensurate in scope with this claim. In particular, the specification failed to enable the skilled artisan to practice the invention without undue experimentation. The quantity of experimentation needed to be performed by one skilled in the art is yet another factor involved in the determining whether "undue experimentation" is required to make and use the instant invention. "The test is not merely quantitative since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." In re Wands, 858 F. 2d 737, 8 USPQ2d 1404(citing In re Angstadt, 537 F.2d 489, 502-04,

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190 USPQ 214, 218 (CCPA 1976)). The skilled artisan would have a numerous amount of modifications to perform in order to obtain substituted compounds as claimed. For these reasons, one of ordinary skill in the art would be burdened with undue "painstaking experimentation study" to determine all the possible substitution of the alcohols and carboxylic acids that would be enabled in this specification.

Based on the unpredictable nature of the invention and state of the prior art and the extreme breadth of the claims, one skilled in the art could not perform the claimed process without undue experimentation, see *In re Armbruster* 185 USPQ 152 CCPA 1975.

Allowable Subject Matter

3. The allowable subject matter is a method of producing analgesia comprising administering a synergistically analgesic effective combination of an opioid analgesic and a compound that binds to the SS1 or SS2 subunit of a sodium channel in a pharmaceutically suitable vehicle, wherein the compound is selected from the group consisting of tetrodotoxin, saxitoxin and a derivatives thereof.

Conclusion

4. No claim is allowed.

5. Claims 1-14 are would be allowable if rewritten to overcome the rejection(s) under 35 U.S.C. 112, second paragraph, set forth in this Office action and to include all of the limitations of the base claim and any intervening claims.

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Any inquiry concerning this communication or earlier communications from the examiner should be directed to Vickie Kim whose telephone number is 703-305-1675.

The examiner can normally be reached on Tuesday-Friday. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Marianne Seidel can be reached on 703-308-4725. The fax phone numbers for the organization where this application or proceeding is assigned are 703-746-3165 for regular communications and 703-746-3165 for After Final communications. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1235.

A handwritten signature in black ink, appearing to be 'Vickie Kim', with a stylized, flowing script.

Vickie Kim,
Patent examiner
August 15, 2003
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